REMARKS/ARGUMENTS

In response to the Office Action of October 3, 2007, Applicants have amended the claims, which when considered with the following remarks, is deemed to place the present application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

The specification has been objected to for allegedly not being arranged according to 37 C.F.R. §1.77(b), including lack of section headings. The abstract has also been objected to for allegedly no mention of the general nature of the compounds of formulas I, II, III or IV or how the compounds will be used in relation to transplantation and autoimmune diseases.

By this amendment, section headings have been added to the specification. The specification has also been amended to indicate the present application is a section 371 application. Further, the abstract has been rewritten on a separate sheet, submitted herewith, to show the general chemical structures of formulas I, III and IV (formula II only differs from formula I in the nature of attached R groups, all of which R groups are defined further in the specification). Accordingly, withdrawal of the objection to the specification is warranted.

Claims 1-10 and 12-14 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly directed to non-enabled subject matter. According to the Examiner, the specification is enabling for treatment of transplant rejection, graft-versus-host disease, and autoimmune disease, but allegedly does not reasonably provide enablement for prevention of these same diseases. In response to the rejection, and solely to advance prosecution of this application, claims 1, 2, and 6 have been amended so that they no longer recite "preventing." Withdrawal of the rejection of claims 1-10 and 12-14 under the enablement provision of 35 U.S.C. §112, first paragraph, is therefore warranted.

Claims 1, 3-8, and 13 have been rejected under 35 U.S.C.§ 102(b) as allegedly anticipated by Heath et al. (US 5,545,636). Heath et al. has been cited for teaching a protein C kinase inhibitor of formula I, II, III and IV with every limitation therein. The reference has also been cited for teaching a method of treating diabetes mellitus by administering to a mammal a protein kinase C inhibitor recited therein.

In response to the rejection, claims 1 and 6 have been amended to recite in relevant part "an autoimmune disease other than diabetes mellitus." Support for the amendment may be found at paragraph [0063] of the published present application, where Heath et al. is specifically

cited as teaching use of protein kinase C inhibitors of formula I, II, III or IV in treating diabetes mellitus. In view of the amendments to claims 1 and 6, withdrawal of the rejection of claims 1, 3-8 and 13 under 35 U.S.C. §102(b) is respectfully requested.

Claims 1-10 and 12-14 have been rejected under 35 U.S.C.§ 103(a) as allegedly unpatentable over Heath et al. as applied to claims 1, 3-8, and 13, above, and in further view of Albert et al. (US 2004.0053949). Heath et al. has been cited for teaching a protein C kinase inhibitor of formula I, II, III and IV with every limitation therein. The reference has also been cited for specifically teaching the compound 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)1H-iondol-3-yl)-pyrrole-2,5-dione, at column 53, Example 68, lines 19-32. The Examiner readily admits that Heath et al. do not specifically teach rheumatoid arthritis as a disease to be treated, nor a composition that includes at least one second agent selected from an immunosuppressant and immunomodulatory drug.

Albert et al. has been cited for teaching protein kinase C inhibitors which can be administered with an immunomodulatory drug. The reference has also been cited for teaching that protein kinase C inhibitors are useful in treating many diseases including rheumatoid arthritis.

According to the Examiner, it would have been obvious to combine the compound of Heath et al. with an immunomodulatory compound and to use the compound of Heath et al. to treat rheumatoid arthritis, since Albert et al. teaches the combination of an immunomodulatory compound with a protein kinase C inhibitor further aids in the treatment of autoimmune diseases and inhibition of protein kinase treats rheumatoid arthritis.

Applicants respectfully traverse the rejection of claims 1-10 and 12-14 under 35 U.S.C.§ 103(a) for the following reasons. Albert et al. teach indolylmaleimide derivatives of formula I, comprising either a substituted phenyl, naphthyl, tetrahydronaphthyl, quinzaolinyl, quinolyl, isoquinolyl or pyrimidinyl residues having interesting pharmaceutical properties, e.g., in the treatment and/or prevention of T-cell mediated acute or chronic inflammatory diseases or disorders, autoimmune diseases, graft rejection or cancer. *See* Albert et al. abstract, pages 1-3.

Applicants respectfully submit that the protein kinase C inhibitors of formula I, II, III and IV recited in the present claims are distinct from, and not suggested by, the indolylmaleimide derivatives of formula I, disclosed by Albert et al.

It is further submitted that one skilled in the art would not be motivated to use a compound of Heath et al. to treat rheumatoid arthritis since Heath et al. teach use of their

compounds in "treating inflammation" but do not describe rheumatoid arthritis as being an inflammatory disease. *See* Heath et al. column 12, lines 1-5.

Paragraph [0221] of Albert et al. teaches the following:

> The compounds of formula I in free form or in pharmaceutically acceptable salt form exhibit valuable pharmacological properties, e.g., inhibiting Protein Kinase C (PKC) e.g., PKC isoforms like α, β, δ, ε, η, or θ activity, inhibiting T-cell activation and proliferation, e.g., by inhibiting production by T-cells or cytokines, e.g., IL-2, by inhibiting the proliferative response of T-cells to cytokines, e.g., IL-2, e.g. as indicated in in vitro and in vivo tests and are therefore indicated for therapy.

At paragraph [0245], Albert et al. teach the following:

> The compounds of formula I are, therefore, useful in the treatment and/or prevention of diseases or disorders mediated by T lymphocytes and/or PKC, e.g., acute or chronic rejection of organ or tissue allo- or xenografts, atherosclerosis, vascular occlusion due to vascular injury such as angioplasty, restenosis, hypertension, heart failure, chronic obstructive pulmonary disease, CNS diseases such as Alzheimer disease or amyotrophic lateral sclerosis, cancer, infectious diseases such as IDS, septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury e.g., myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, or traumatic shock. *The compounds of formula I are also useful in the treatment and/or prevention of T-cell mediated acute or chronic inflammatory diseases or disorders or autoimmune diseases, e.g., rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus....*

As the cited passage immediately above indicates, Albert et al, ascribe various properties to their indolylmaleimide derivatives of formula I. Although Albert et al. teaches treatment and/or prevention of diseases or disorders mediated by PKC, *rheumatoid arthritis is not one of them.* Rather, Albert et al. teach that their compounds of formula I can treat T-cell mediated acute or chronic inflammation such as rheumatoid arthritis. Thus, contrary to what the Examiner has asserted on page 12, lines 17-20 of the office action, Albert et al. do *not* teach that inhibition of protein kinase C treats rheumatoid arthritis.

At paragraph [0255], Albert et al. teach that the compounds of formula I may be administered as the sole active ingredient "or together with other drugs in immunomodulating regimens or other anti-inflammatory agents e.g, for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders." Applicants submit that the extent of teaching provided by this aspect of Albert et al., is that a compound of formula I of Alberts et al. may be combined with another drug in treating an autoimmune disorder such as rheumatoid arthritis.

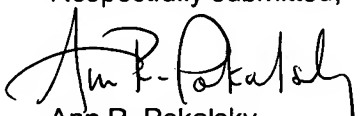
Summarizing, Heath et al. teach use of the compounds recited in the present claims in treating inflammation. *See* Heath et al. column 12, lines 6-8. Albert et al. teach a completely different class of compounds from Heath et al., which mediate acute or chronic inflammatory disorders *or autoimmune disorders such as rheumatoid arthritis.*

In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).

One skilled in the art having both Heath et al. and Albert et al. in hand, would not consider using a compound taught by Heath et al. to treat rheumatoid arthritis, either alone or in combination with another drug, because there is no indication in either Heath et al. or Albert et al. that the various compounds disclosed therein are equivalents for treating an autoimmune disease such as rheumatoid arthritis. Applicants' disclosure at paragraph [0067] is the first disclosure that the compounds disclosed in Heath et al. may be used for treating an autoimmune disease such as rheumatoid arthritis. Accordingly, the rejection of claims 1-10 and 12-14 under 35 U.S.C.§103(a) is in error and should be withdrawn.

In view of the foregoing amendments and remarks hereinabove, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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